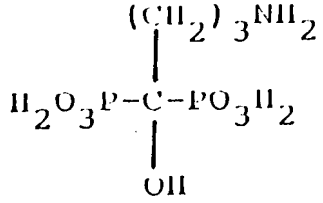
by this amendment has been drafted as agreed during the conference.

The Examiner rejected Claim 14 of this application because of the Chemical Abstracts 96 52503 (1982) reference. In view of the presentation of new Claim 15, it is believed that this reference is totally inapplicable.

The Chemical Abstracts reference shows the compounds of formula

$$NH_2(CH_2)_nC[P(O)(OH)_2]OH$$

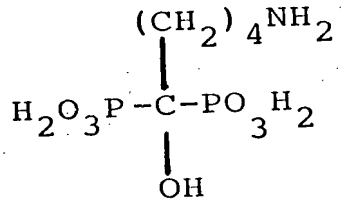
and merely states that they are useful as sequestering agents. The Examiner noted that the compound 4-amino-1-hydroxy-butane-1,1-biphosphonic acid, (AHbuBP) of structure hereinbelow:



is within the scope of the reference. The Examiner then concluded that a composition claim is not different from a claim on the compound itself. In view of the fact that Claim 15 covers a method of treatment, this rejection is now moot.

The use of sequestering agents in the reference certainly does not lead one to conclude that the compound will be useful in the treatment of urolithiasis and in the inhibition of bone reabsorption. Applicants have compared the

compound with 5-amino-1-hydroxy-pentan-1,1-biphosphonic acid (AHPeBP) of structure



and the known 6-amino-1-hydroxyhexane-1,1-biphosphonic acid (AHEXBP) prepared according to Italian Patent Application No. 19673 A/81 and with the known dichloromethanebiphosphonic acid (Cl_2MBP).

The data reported show that AHPEBP is the most active in inhibiting the bone reabsorption but manifests some toxicity at a higher dosage. The compound AHEXBP is also active on the reabsorption and is superior to Cl_2MBP. A significant difference is with respect to the mineralization because AHEXBP induces strong inhibition in the dose of 10 mg of P/kg while AHBUBP has no effect or only a slight effect or only an effect to a very small extent.

These results show that the amino compounds with an odd number of carbon atoms are somewhat toxic but are much more active in inhibiting the bone reabsorption (pages 24-27). The compounds with an even number of carbon atoms have an activity slightly superior to Cl_2MBP. Another significant fact is that AHBUBP does not induce or induces only to a very small extent the inhibition of mineralization at high dosage while AHEXBP exhibits high inhibition. Consequently, AHBUBP appears to more suitable for use in diseases with an increase reabsorption of bone in humans.

Applicants have carried out extensive clinical studies. The substance AHBUBP has been tested in primary hyperparathyroidism. A drastic reduction of calcemia was achieved up to normal values in five of the seven patients. The decrease of calcemia has been accompanied by a rapid and parallel decrease of hydroxyprolinuria and decrease of the urinary excretion of calcium. In three cases, the administration of 25 mg/day of the substance for seven days has brought the normalization of calcemia up to the day of surgical intervention of removal of the parathyroidal adenoma. In four other patients treated for a shorter period of time, only 3-4 days and with a dose of 4-8 mg/day, the decrease of calcemia has been transitory, with the values of calcemia and the hydroxyprolinuria having a tendency to return to the basal values a few days after the suspension of the drug. The Examiner has not questioned these data.

Three patients with Paget's disease were treated with AHBUBP in the dose of 4 mg. in one patient and 0.5mg in the case of the other two patients per day, for a period of 8 and 21 days respectively. In all the three patients, a normalization of the urinary excretion of hydroxyproline was achieved. After 6-8 months, the three patients still exhibit normal values of hydroxyprolinuria and alkaline phosphatemia.

On page 30, line 5 et seq., applicants have stated that AHBUBP inhibits bone reabsorption and is about 100-300 times more active than Cl_2MDP. The two substances differ also with respect to the mechanism of action: the activity on the immunity system appears to be peculiar to AHBUBP.

The Examiner has not taken issue with the conclusion in Dr. Rosini's declaration that amino derivatives (amino-propane; amino-butane) are more active than other diphosphonates and that AHBUBP has an activity more than 100 times higher than that of Cl_2MBP (Clodronate).

Dr. Rosini also reports (see declaration, page 2, last paragraph) that AHBUBP displays a surprisingly and unforeseeably longer activity than Cl_2MDP. Indeed the substance, in a 5-6 day treatment, causes positive effects which last for weeks or months after treatment. On the other hand, Cl_2MBP must be administered continuously in order to maintain the therapeutic effect.

The extensive data in Dr. Rosini's declaration show that in the case of eight patients affected by multi mieloma (MM) with diffused osteolytic lesions and strong bone pains, treatment with AHBUBP in a dose of 2.5 mg i.v./ die for 5 days every third-fourth month, resulted in a remarkable improvement or disappearance of bone pains within the first 5-6 days from the beginning of the administration. Hydroxyprolinuria, calciuria, hypercalcemia, main symptoms of bone reabsorption, which were high before the treatment, reached normal limits during and after the administration.

87

The progress of osteolitic lesions ceased and sometimes their extension decreased; there is also evidence of the recomposition of pathologic fractures in 2 cases. No side effects were observed.

In conclusion, the superiority of 4-amino-1-hydroxy-butan-1,1-biphosphonic acid over other biphosphonates has not been questioned by the Examiner. No one, prior to the present invention, had suggested the use of the substance for pharmaceutical and medical use. The Chemical Abstracts reference did not suggest such a use.

In view of the fact that a single claim is now present in this application and that Claim 15 has been drafted as agreed during the conference, a prompt notice of allowance is respectfully urged. If any additional matter is needed to place this application in condition of allowance, the Examiner is respectfully urged to contact the undersigned at the telephone number indicated hereinbelow.

Respectfully submitted,

BUCKNAM AND ARCHER

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